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tDCS over the motor cortex improves lexical retrieval of action words in post-stroke aphasia

Meret Branscheidt[1,2]*$, Julia Hoppe[3]*, Pienie Zwitserlood[4], Gianpiero Liuzzi[1,3]

[1]University Hospital Zurich, Department of Neurology, Zurich, Switzerland
[2]Johns Hopkins University, Department of Physical Medicine and Rehabilitation, Maryland, USA
[3]University Medical Center Hamburg-Eppendorf, Department of Neurology, Hamburg, Germany
[4] University of Münster, Department of Psychology, and Otto Creutzfeldt Center for Cognitive and Behavioral Neuroscience, Münster, Germany

*Both authors contributed equally to the present manuscript.
$Corresponding author

Address correspondence to:
Dr. med. Meret Branscheidt
Email: mbransc1@jhmi.edu
Frauenklinikstr. 26
8091 Zürich
Schweiz
+41 43 253 0307

Abstract

One-third of stroke survivors worldwide suffer from aphasia. Speech and language therapy (SLT) is considered effective in treating aphasia, but due to time constraints, improvements are often limited. Non-invasive brain stimulation is a promising adjuvant strategy to facilitate SLT. However, stroke might render "classical" language regions ineffective as stimulation sites.

Recent work showed the effectiveness of motor-cortex stimulation together with intensive naming therapy to improve outcomes in aphasia (Meinzer *et al.*, 2016). Although this study highlights the involvement of the motor cortex, the functional aspects by which it influences language remain unclear. In this study, we focus on the role of motor cortex in language, investigating its functional involvement in access to specific lexico-semantic (object- vs. action relatedness) information in post-stroke aphasia.

To this end, we tested effects of anodal tDCS to the left motor cortex on lexical retrieval in 16 patients with post-stroke aphasia in a sham-controlled, double-blind study design. Critical stimuli were action & object words, and pseudowords. Participants performed a lexical-decision task, deciding whether stimuli were words or pseudowords. Anodal tDCS improved accuracy in lexical decision, especially for words with action-related content and for pseudowords with an "action-like" ending ($t_{15} = 2.65$, $p = 0.036$), but not for words with object-related content and pseudowords with "object-like" characteristics. We show as a proof-of-principle that the motor cortex may play a specific role in access to lexical-semantic content. Thus, motor-cortex stimulation may strengthen content-specific word-to-semantic concept associations during language treatment in post-stroke aphasia.

New and Noteworthy

The role of motor cortex (MC) in language processing has been debated in both health and disease. Recent work has suggested that MC stimulation together with speech-language therapy enhances outcomes in aphasia. We here show that MC stimulation has a differential effect on object- and action-word processing in post-stroke aphasia. We propose that MC stimulation may specifically strengthen word-to-semantic concept association in aphasia. Our results potentially provide a way to tailor therapies for language rehabilitation.

Introduction

Approximately one third of stroke patients suffer from aphasia. Aphasia impedes the ability to understand spoken language, read, write or speak. The occurrence of aphasia is strongly associated with post-stroke depression and impaired quality of life (De Ryck *et al.*, 2013; Engelter *et al.*, 2006; Hilari, 2011; Wade *et al.*, 1986). Only intense treatment of 5-10 hours speech and language therapy per week significantly improves language recovery in the chronic stage after stroke (Bhogal *et al.*, 2003; Breitenstein *et al.*, 2009). Yet, due to economic and logistic constraints, hardly any aphasic patient receives such extensive training, as language rehabilitation is restricted to 1-5 hours per week, even in economically developed countries (Code and Petheram, 2011). Thus, ancillary therapeutic strategies such as non-invasive brain stimulation have been gathering attention. TDCS is a technique by which brain functions can be temporarily and non-invasively modulated. It has been applied in several studies on language recovery, and probed as possible adjuvant to influence different aspects of language processing (Baker *et al.*, 2010; Flöel *et al.*, 2008; Hamilton *et al.*, 2011; Holland and Crinion, 2012; Monti *et al.*, 2013). Although some studies showed promising results, a recent general meta-analysis of tDCS application after stroke could not confirm a definitive effect of tDCS on "activities in daily living" (ADL) measures (Elsner *et al.*, 2013). Most studies on aphasia applied stimulation to lesioned and perilesional brain sites, and investigated vocabulary learning or picture naming, mainly with object-related stimuli. However, evidence suggest that other brain sites (e.g. the intact right hemisphere) can also have the potential to promote language recovery after stroke. At present there is no consensus about the best stimulation site and/or time to achieve optimal therapeutic results (Hamilton, Chrysikou, & Coslett, 2011). Furthermore, it is unclear whether different stimulation sites may differentially affect specific components of language function (Hamilton et al., 2011). In a recent study combining high-intensity naming training with simultaneous administration of anodal tDCS to the motor cortex, Meinzer and colleagues demonstrated meaningful and long-lasting improvement of performance in post-stroke aphasic patients (Meinzer, Darkow, Lindenberg, & Flöel, 2016). However, it is unknown whether tDCS stimulation of the motor cortex is able to influence and modulate functional aspects of specific lexico-semantic networks in post-stroke aphasia.

Current theories on semantic processing posit that access to a word's meaning involves a distributed network comprising "classic" perisylvian language regions and distant, extrasylvian brain regions (Barsalou, 2008; Fischer and Zwaan, 2008; Mahon and Caramazza, 2009; Patterson *et al.*, 2007; Pulvermüller, 1999; Pulvermüller, 2005). These theories gained support from neuroimaging studies with healthy participants, and investigations in patients with focal brain lesions, which showed an involvement of the motor cortex (MC) during the processing of action words (Aziz-Zadeh *et al.*, 2006; Damasio *et al.*, 1996; Glenberg *et al.*, 2008; Hauk *et al.*, 2004; Kemmerer *et al.*, 2008). Stimulation of the MC can facilitate lexical retrieval in healthy elderly (Meinzer *et al.*, 2014), and has a specific differential impact on distinct lexical content, suggesting a functional role of the MC in processing word meanings related to actions and motor activity (Pulvermüller 2005). Moreover, it could be demonstrated that stimulating the MC affects learning of a novel action vocabulary (Liuzzi *et al.*, 2010).

Thus, stimulation of the MC could indeed offer an alternative strategy to influence language function. Yet, as argued above, the motor cortex may play a specific role in linguistic processing, enhancing the processing of some but not all semantic content. To shed light on this combination of questions, we investigated whether tDCS to the MC facilitates lexical decisions in aphasic patients. Therefore, we hypothesized that tDCS to the MC specifically facilitates processing of action- compared with object-related words, as observed in young adults (see above).

Methods

Patients

A total of 16 patients with aphasia caused by first-ever ischemic stroke were enrolled in the study protocol: mean age 61.1 ± 10.2 years, age range: 47-78 years. None of the patients had a stroke in the right hemisphere. All patients were native German speakers. With the Aachener-Aphasie-Test (AAT), five patients were diagnosed with Broca's aphasia, six patients with amnestic aphasia and one patient with global aphasia. The remaining five did not fulfill the criteria of aphasia of the AAT, but had persistent mild language problems, such as slowing of speech, occasionally occurring paraphasia, or naming problems. Additional inclusion requirements were integrity of the primary MC as established with CT or MRI scans, and the absence of alexia. For patients' specifics, see Table 1.

Exclusion criteria comprised more than one stroke in medical history, additional neurological diseases, contraindications for transcranial magnetic stimulation (e.g. history of epileptic seizure, metal implants in the head/neck region or pacemaker implantation), and use of illegal or neuroactive (e.g. antidepressants, anticonvulsants etc.) drugs as assessed by a standardized questionnaire and a medical history taken by an experienced neurologist.

Lexical decision task (LDT)

The lexical decision task was used instead of naming, which poses differential difficulty depending on the type of aphasia. Lexical decision is known to tap into lexical and semantic information (Chumbley and Balota, 1984) and shows very similar brain activation patterns than naming (Carreiras et al., 2007). Pseudowords and existing words of the German language were presented to the patients in random sequence on a computer screen (white letters on black background, font size 76, typeface Arial). Participants had to decide whether the given word was a real German word (“yes”) or not (“no”) by pressing one of two buttons on a custom-made button box, with two fingers of the left hand (left button for “yes”, right button for “no”).

We selected German verbs related to hand actions (f. e. to type, to wave), and German nouns related to objects (f. e. table, flower) that did not have meanings associated with actions or movement. Action and object words were balanced regarding word length (6-9 letters, mean length 7 letters for both groups), number of syllables (only disyllabic words) and word frequency using the Celex database (Baayen *et al.*, 1995; www.celex.mpi.nl) (mean frequency 3 ± 4,09 standard deviation for object words, and 3 ± 4,06 for action words; Student t-test action words vs. object word n. s.). Pseudowords were generated by changing the position of characters of the German words (e.g. SATTEL (German noun for saddle) to LASETT (pseudoword)), resulting in the same characters and number of syllables. “Action-like” pseudowords (ALP) all had a word ending typical for the infinitive form of German verbs/action words (like: -en; -ern; -eln).

Words and pseudowords were presented for 2 s, with a varying inter-trial interval (ITI of 3–5 s (see Fig. 1). Patients were required to respond as quickly as possible by pressing one of two buttons. Responses exceeding 2 s after trial onset were classified as missing answers. The test session consisted of 160 stimuli (German action and object words and their pseudoword counterparts, 40 stimuli in each group) split into four blocks (each block 40 words), for practice trials see below. There was a fixed break of two minutes between all blocks. The experiment lasted approximately 22 min. For the lexical decision task, reaction time and response accuracy (number of correct decisions) were collected as outcome measures. For a complete list of words see Table 2.

Simple Reaction Time Task

A simple reaction time task (sRT) assessed whether tDCS had an effect on attention and alertness. Patients had to respond as quickly as possible by pressing one button on the same custom-made button box with their left middle finger to a red cross presented on a computer screen. The sRT consisted of 30 trials with randomly varying inter-trial intervals between 4-6 s to avoid anticipation. The overall duration was approximately 2.5 min.

Transcranial Direct Current Stimulation

To locate the patient's cortical hand area in the left primary MC ("hot spot"), we used transcranial magnetic stimulation (TMS) before applying tDCS. TMS was administered by a Magstim 200 stimulator connected to a figure-8-shaped coil (7 cm in diameter). Motor-evoked potentials (MEPs) were recorded from the right hand using surface electrodes placed over the first dorsal interosseus muscle. The "hot-spot" in the left MC was determined according to standardized procedures (Rossini *et al.*, 1994) and chosen for the placement of the stimulating tDCS electrode. In one patient (patient ID 3), no MEP could be evoked in the right arm. In this patient, the mirror equivalent of the "hot spot" in the right hemisphere was chosen for tDCS application to the MC of the left hemisphere.

TDCS was applied via two sponge electrodes soaked in a 0.9% saline-solution and connected to a DC-stimulator (Eldith®, serial no. 0006). The stimulating anodal electrode (Eldith®, 5x5 cm, surface area 25 cm^2) was placed over the "hot-spot" of the left MC. The reference electrode (7x5 cm, surface area 35 cm^2) was positioned over the right supraorbital region. Electric current was set to increase slowly in a ramp-like fashion over 10 s, until 2 mA were reached. This stimulation procedure usually elicits a transient tingling sensation over the scalp for a few seconds (Gandiga *et al.*, 2006). For verum stimulation, 2 mA constant current were delivered for 20 min. For sham stimulation, the same current intensity was delivered for only 30 s. At the end of both verum and sham stimulation, the current was continuously decreased to zero over 10 s. This approach is regarded as a safe stimulation procedure (Nitsche *et al.*, 2008) and as a reliable blinding method (Gandiga *et al.*, 2006). We evaluated perception of unpleasant sensations (discomfort and pain), fatigue and attention with questionnaires using visual analogue scales (VAS).

Experimental design

TDCS was employed in a block-randomized, double-blind, sham-controlled, cross-over design. Subjects were familiarized with the lexical decision task (LDT) in a practice session D1 using a shorter version of the task (10 trials without words that were used for the test sessions). The first test session D2 and the second test session D3 were performed with an interval of 7 days. The stimulation type (anodal or sham tDCS) was allocated randomly to session D2 or D3 for each patient. Two stimulus sets (each with 160 different words) for the lexical decision task were utilized. Prior to randomization, a list with counterbalanced order of stimulation type and stimulus set was composed for the 16 patients. The "RAND" function of Excel was used to create a random number for each patient, this numbers were then sorted by sizes in descending order and assigned to the patient list created before. tDCS stimulation (anodal and sham) was turned on by a third person not involved in the remainder of the experiment. The sRT task was performed three times in one session: prior to TMS, immediately after tDCS application started (before the first LDT block), and after the LDT. In each test session, tDCS (anodal or sham) started with the sRT. Anodal tDCS lasted for 20 min. As the lexical decision task took about 22 min and the preceding sRT took 2.5 min, verum stimulation was applied during 80% of the LDT. Given that the neurophysiological effects of anodal tDCS with 2mA over the motor cortex outlast the actual stimulation period for up to 90 min (Batsikadze, Paulus, Kuo, & Nitsche, 2013), a stimulation period of 20 min was regarded as sufficient to cover both tasks. Please see Fig. 1 for details of the study design.

Statistics and Data Analysis

Primary outcome measures of the LDT were reaction time (RT) and accuracy of decisions (correct rejection of pseudowords, correct acceptance of existing German words, given as percentage of all possible correct answers). Before application of parametric tests, normal distribution of the dependent variables was tested using graphical methods (histograms and quantile-quantile plots) and Shapiro-Wilk tests. As result of this analysis, reaction times of the sRT were log transformed. Differences between stimulation conditions for RT and accuracy were analyzed using a three-factorial repeated measures analysis of variance (rmANOVA) (within-subject factors “stimulation” [two levels: anodal, sham], “word class” [two levels: action words, object words] and “stimulus type” [two levels: real word, pseudoword]). Given the clinical heterogeneity in our patient cohort, outcome measures of patients were additionally compared according to their type of aphasia identified by the AAT (Broca’s aphasia (N = 5), amnestic aphasia (N= 5), mild residual language deficits (N = 5), patients with a mixed clinical presentation were assigned according to their prevalent deficit: between-subject factor “aphasia type” [three levels: broca, amnestic, mild residuals]). Data for the single patient with global aphasia were not included in the analysis.

Mauchly test of sphericity and Greenhouse-Geisser correction were applied where appropriate. Data are expressed as mean ± standard error. Statistical analyses were done using SPSS 15.0 ® and GraphPad Prism® Software. To evaluate the influence of tDCS stimulation on simple reaction time (sRT) a two-factorial rmANOVA (within-subject factors “stimulation” [two levels: anodal, sham] and “time point” [three levels: pre-test, during stimulation, post-test]) was performed. Student’s two-tailed t-test were applied to compare the results of the visual analog scales regarding unpleasant sensation of the stimulation (discomfort and pain) and fatigue. Bonferroni-corrected two-tailed t-tests were used for all post-hoc comparisons. Results were considered significant at a level of $p < 0.05$. Corrected p-values are given in the results section.

Ethics Statement

The study protocol was approved by the local ethics committee of the University Medical Center Hamburg-Eppendorf (PV3128) and was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki; http://www.wma.net/e/policy/b3.htm). All patients gave written informed consent to participate in the study protocol.

Results

Reaction time: lexical-decision task

Patients overall mean reaction time was 1213.0 ± 94.0 s. Trials that exceeded the time window of 2 s amounted to less than 0.2%, and never exceeded 2% within a single test session. Anodal tDCS stimulation to the MC did not influence overall lexical decision times. There was neither a significant main effect nor any interaction of the factor “stimulation” with the other factors (stimulation: $F_{0,15}$ = 1.029, p = 0.372; stimulation*word class: $F_{0,15}$ = 0.945, p = 0.346; stimulation*stimulus type: $F_{0,15}$ = 0.025, p = 0.877; stimulation *word class*stimulus type: $F_{0,15}$ = 0.063, p = 0.805), see Fig. 2. The main effects of “word class” (object/action words) and of “stimulus type” (real word/pseudoword) were significant (word class: $F_{0,15}$ = 12.665, p = 0.003; stimulus type: $F_{0,15}$ = 13.389, p = 0.002) indicating faster reactions to object words than to action words (1185.0 ± 87.2 s versus 1240.9 ± 100.5 s, t_{63} = 3.63, p = 0.003) and to real words than to pseudowords (mean = 1090.9 ± 56.3 s versus 1335.0 ± 112.9 s, t_{63} = -6.85, p < 0.001). Moreover, there was a significant interaction of “word class*stimulus type”, with a large 100 ms difference in RT between “action-like” ALP and “object-like” OLP pseudowords (longer reaction times for ALP than for OLP), but only a small and insignificant difference between action and object words.

The latencies from the control simple reaction time task (sRT) showed no significant differences for the factors time point ($F_{0,15}$ = 2.275, p = 0.152), stimulation ($F_{0,15}$ = 2.1, p = 0.14), nor an interaction of stimulation*time point ($F_{0,15}$ = 0.692, p = 0.508; pre-sham: 291.8 ± 32.7 s and -anodal: 276.9 ± 30.7 s, during-sham: 284.4 ± 35.2 s and -anodal: 267.6 ± 26.9 s, post-sham: 287.9 ± 31.8 s and -anodal: 285.8 ± 30.5 s).

Accuracy

Independent of the stimulation group, accuracy differed significantly as a function of word class and stimulus type (word class: $F_{0,15}$ = 30.963, p < 0.001; stimulus type: $F_{0,15}$ = 5.666, p = 0.031). Accuracy was higher for object than for action words (92.8% ± 0.96 versus 86.8% ± 0.16, t_{15} = -5.56, p < 0.001), as well as for real words than for pseudowords (92.9% ± 0.45 versus 86.6% ± 2.1, t_{15} = 2.38, p = 0.031). Word class and stimulus type interacted regarding accuracy rates

($F_{0,15}$ = 12.456, p = 0.003), resulting from lower accuracy for "action-like" pseudowords ALP (81.3%) than for all other conditions: OLP 92.0%, real object words 93.6%, real action words 92.3%, which did not differ from each other (ALP words vs. real action words, t_{15} = 2.9, p = 0.004; ALP vs. OLP, t_{15} = 4.95, p = 0.004; ALP vs. real object words, t_{15} = 2.72, p = 0.003; all other comparisons n. s.).

There was a significant main effect of tDCS on overall accuracy ($F_{0,15}$ = 5.805, p = 0.029) with higher accuracy under anodal than sham stimulation (91.1% ± 1.62 versus 88.5% ± 1.81). This was qualified by a significant two-way interaction of stimulation with word class ($F_{0,15}$ = 5.117, p = 0.039): Anodal tDCS led to improved accuracy rates for action stimuli, (anodal/action words and ALP 88.6% ± 2.06 versus sham/action words and ALP 84.9% ± 2.25; t_{15} = 2.65, p = 0.036), whereas no such effect was detected for object stimuli (anodal/object words and OLP 93.4% ±1.3 versus sham/ object words and OLP 92.5% ± 1.43; t_{15} = 1.28, p = 0.438, see Fig. 3). There was no two-way interaction of stimulation*stimulus type nor a three-way interaction of stimulation*word class*stimulus type (stimulation*stimulus type: $F_{0,15}$ = 2.397, p = 0.142; stimulation*word class*stimulus type: $F_{0,15}$ = 0.944, p = 0.347).

Results of questionnaires addressing perception of unpleasant sensations (i.e. discomfort/pain) as well as fatigue and attention did not reveal any significant differences as a function of stimulation conditions. Mean value for discomfort on the VAS for anodal tDCS 2.5 vs. 2.7 under sham (t_{15} = -0.77, p = 0.453), mean value for pain 1.4 vs. 1.9 under sham (t_{15} = -1.96, p = 0.069), mean value for fatigue 2.4 vs. 3.1 (t_{15} = -1.52, p = 0.149), mean value for attention 2.5 vs 2.8 (t_{15} = -0.79, p = 0.441).

Comparison between different types of aphasia

This analysis indicated an interaction for reaction times between word class*aphasia type: $F_{2,12}$ = 7.784, p = 0.007. While reaction times for object words were lower in all three types of aphasia, this difference only reached significance for amnestic aphasic patients ($t_{1,19}$ = 3.361, p = 0.003).

Interestingly, there was a three-way interaction for accuracy between aphasia type*word class*stimulus type ($F_{2,15}$ = 3.928, p = 0.049), and a four-way interaction between aphasia type word class*stimulus type*stimulation* ($F_{2,15}$ = 4.438, p = 0.036). Amnestic patients showed only small differences in accuracy between real and pseudowords, both for action and objects words. In contrast, patients with Broca's aphasia and mild aphasia showed larger differences between action-related real and pseudowords than between object-related real and pseudowords. Looking at the four-way interaction, these differences became smaller only under anodal stimulation.

However, none of the post-hoc comparisons were significant, probably due to the small sample size.

Discussion

The aim of the present study was to investigate whether anodal tDCS stimulation to the motor cortex would enhance lexical access in a group of chronic aphasic patients. Whereas no specific effects of tDCS on lexical decision latencies were observed, the results show that anodal stimulation to the MC of the language-dominant hemisphere improves overall accuracy in a lexical decision task. Importantly, improvement in decision accuracy was depended on the meaning of the words: lexical decisions were significantly more accurate under anodal stimulation for action words and "action-like" pseudowords (ALP), while object words and "object-like" pseudowords (OLP) were not significantly affected by tDCS.

The pattern of results corroborates previous studies showing an involvement of the left MC in action-word comprehension and learning (Aziz-Zadeh *et al.*, 2006; Hauk *et al.*, 2004; Kemmerer *et al.*, 2008; Liuzzi *et al.*, 2010). We here provide – to the best of our knowledge - first "proof-of-principle" evidence for patients with post-stroke aphasia that the left MC is involved in lexico-semantic access, in particular in processing action words. In the following, we discuss three main aspects that may explain the role of the left MC in lexical retrieval: 1) The MC may contribute to the semantic network (according to the distributed semantics hypothesis). 2) Raised activity in premotor regions may facilitate detection of ortho-phonological cues as "action-like" endings. 3) motor pre-activation may engage in lexical retrieval independent of word class and word meaning.

1) Lexico-semantic access in aphasia patients

Access to word meaning is an important core function of language. It is the binding element between the word level and semantic concepts. Access to the meaning of a word minimally requires two types of information: a) word-form information, that is, phonological (sound of a word) and/or orthographic (how a word is written) information and b) semantic-conceptual information that codes for the meaning. It has been reported that patients with frontal lesions have more often difficulty in comprehending action words, whereas temporal lesions are associated with an impaired access to object words. While this double dissociation has been repeatedly reported, recent reviews of the literature revealed rather inconsistent results (Crepaldi *et al.*, 2011). Language processing relies on widespread, interconnecting networks rather than circumscribed, topographically clearly distinguishable brain regions (Friederici, 2011). With regard to semantics, some theories posit that the meaning of words is stored in brain regions distributed across both hemispheres, also outside the “classical” language areas (Binder and Desai, 2011; Mahon and Caramazza, 2009; Patterson *et al.*, 2007; Pulvermüller, 2013). It could be shown that passive reading of action words that referred to face, arm or leg movements resulted in activation along the motor cortex in the same regions that are activated when the actual movement was performed, suggesting a somatotopic contribution of motor cortex to action-word meaning (Hauk, Johnsrude, & Pulvermüller, 2004). Evidence for the functional significance of the link between language processing and motor cortex activation was provided by the same group. Using TMS, Pulvermuller and colleagues observed that stimulation over the motor area for the hand solely influenced processing of hand-related action words (e.g. to pick) but not of leg-related action words (e.g. to kick) while the opposite was true for stimulation of leg motor areas (Hirschfeld & Zwitserlood, 2012; Pulvermüller, Hauk, Nikulin, & Ilmoniemi, 2005).

In stroke patients, large parts of the brain regions containing information related to the meaning of a word (e.g. knowledge about animals, fruits, colors, actions etc.) may still be preserved, whereas the connection to the word level may have been disturbed by the stroke lesion. Word forms are assumed to draw upon left-hemispheric perisylvian neuronal circuits, which connect with sensorimotor and perceptual brain regions and form “cell assemblies” binding the lexical and semantic properties of a word (Pulvermüller, 1999). For action words, it has been proposed that the lexico-semantic circuits include the MC, where action schemata are stored (Fischer and Zwaan, 2008; Pulvermüller, 2005).

Our results are in line with the assumption that access to the meaning of action words involves motor cortical regions in post-stroke aphasia. Based on probabilistic theories, the association of a word form to its related content, e.g. a bodily action, is dependent on frequent co-occurrence of the action and the word form, resulting in robust connections according to Hebbian learning model. In a previous study, we showed that learning a novel word that frequently co-occurs with a specific action leads to a robust connection between the newly learned word and the associated content (Liuzzi *et al.*, 2010). Interfering with motor cortical activity hampers these newly established routes. Repetto et al. found that processing hand-related action words, but not abstract words, was impaired after rTMS to the left primary MC (Repetto *et al.*, 2013). The connections between perisylvian brain regions and the left MC may be weakened after a stroke. In our present study, it could well be that the effect of tDCS to the MC on action words is accomplished by raising weakened connections of the lexico-semantic cell assemblies above a critical threshold. However, the strong effect on pseudowords with “action-like” endings is intriguing in this context. It strongly suggests that tDCS to the MC has a more complex effect on lexico-semantic processing than previously assumed.

2) The relevance of orthographic-phonological cues for lexico-semantic access

The pattern of results obtained in the present study indicates a dissociation between ALP and OLP. Interestingly, both accuracy and reaction times were different between the two types of pseudowords that were matched for length and number of syllables. As the used pseudowords should not elicit any particular semantic associations, orthographic-phonological cues such as the ending of a pseudoword may already lead to different access search strategies to the lexico-semantic networks. We thus assume that after identifying particular orthographic-phonological cues, this information – which in case of ALPs consist of existing morphemes such as –en or –ern, indicating verb status - is routed to semantic networks that code the type and meaning of a word. The dissociated effect of tDCS on pseudowords with "action- and object-like" characteristics suggests differential processing pathways. In German, all verbs in infinitive form end with "-n", "-en", "eln" or "ern" (Duden, 2009) which thus serve as valid cues to verb status. According to our results, ALPs require more processing time than the OLPs. This suggests that upon processing word-form information, potential action words and potential object words recruit different resources. The preferential effect of motor cortical tDCS on ALP suggests that the additional resources are likely to be located outside classic language regions. Only recently, it could be demonstrated that processing pseudowords with "action-like" endings activate motor cortical regions, especially premotor areas, similar to real manual-action words and the actual execution of hand movements. This was not found for real-object words and pseudowords with "object-like" endings (de Zubicaray *et al.*, 2013). We thus conclude that lexical processing of action words (real verbs) and "action-like" words (pseudowords with "action-like" endings) involves neural connections with motor cortical regions. It remains an open question whether the effect of tDCS on action words and ALP reflects semantic or also lexical-grammatical networks. It may well be that the semantic network is intertwined with the network defining grammatical function (Pulvermüller *et al.*, 2012), or that semantic and grammatical aspects of words (such as their word class, or gender) are linked within the lexical representation (Levelt *et al.,*1999). However, this remains an open question at this stage of research and exceeds the scope of the present study.

3) tDCS effects on lexical decisions independent of word class and word meaning

Another explanation for the observed effect of tDCS to the left MC observed here could be global facilitation of lexico-semantic networks by motor pre-activation. There is accumulating evidence for an influence of language perception/processing on cortical excitability of the motor system (Fadiga *et al.*, 2002; Flöel *et al.*, 2003; Liuzzi *et al.*, 2008). One of the basic tenets of this work is the assumption of bidirectionally operating neuronal circuits encompassing “classic” language and motor areas. These bidirectional lexicosemantic circuits can thus be affected by motor pre-activation and facilitate word retrieval in aphasic patients. Relevant evidence has been provided by Meinzer et al., who observed that motor pre-activation by standing facilitated word retrieval in aphasic patients, compared with sitting (Meinzer *et al*., 2011). This and other studies {Hanlon:1990tu, Marangolo:2010fl, Hirschfeld:2012cj} also showed an effect of motor pre-activation using picture-naming tasks that required overt speech production. Two of these studies used pictures of everyday objects (Hanlon *et al.*, 1990; Meinzer *et al.*, 2011), the other two tested verb retrieval using photos of actions (e.g. kissing) {Marangolo:2010fl, Hirschfeld:2012cj}. Taking into account that premotor and inferior frontal regions may specifically engage in phonological working memory and lexical retrieval (Binder, 2005), one explanation could be that raising motor cortical excitability may result in more efficient processing in brain regions subserving phonological processing and lexical retrieval in general. We here show that raising excitability in the left MC may specifically facilitate lexical access to action words, but we obtained no effects for object words. This differential effect rather suggests a specific effect of the MC on specific semantic or grammatical categories.

The potential therapeutic use of frontal and motor cortical tDCS in post-stroke aphasia

Several studies have investigated the impact of non-invasive brain stimulation to the frontal region in aphasic patients testing different linguistic functions from straightforward picture naming to spontaneous speech (Marangolo *et al.*, 2013; Elsner *et al.*, 2013; Holland and Crinion, 2012). Concerning action versus object processing, effects could be shown for both word classes in different language tasks, for healthy and brain damaged subjects (Holland *et al.*, 2011; Baker *et al.*, 2010; Cappa *et al.*, 2002; Cotelli *et al.*, 2011).

Few studies addressed the effect of tDCS applied to frontal areas on action-word processing in stroke patients. Marangolo et al. demonstrated that only anodal stimulation over Broca’s area, but not over Wernicke’s area, nor sham stimulation led to higher response accuracy in an action-naming task after intensive language training (Marangolo *et al.*, 2013). Fiori et al. showed reliably improved verb naming in aphasic patients after anodal tDCS stimulation to the frontal area, whereas object naming showed a greater improvement after stimulation over the temporal region (Fiori *et al.*, 2013).

In the present study, we show that specific linguistic functions can be improved by non-invasive brain stimulation to primarily motor brain regions that are often intact in aphasic patients and can be easily located even without prior neuroimaging.

The role of motor cortical regions for lexico-semantic access has been long debated in both health and disease. We here show a clear distinction of MC stimulation on object and action words in post-stroke aphasia. Interestingly, stimulation affected both the identification of real action words and pseudowords with "action-like" endings, suggesting a facilitation of lexico-semantic access by morpheme-sized orthographic/phonological information. The focus of our study was to investigate the mechanistic aspects of how motor cortex stimulation influences language function in aphasic patients. However, future research will have to determine whether the reported effect generalizes to other language tasks (e.g. naming tasks) and can be linked to the clinical improvements in communication reported recently for the combination of SLT and motor cortex stimulation (Meinzer et al. 2016).

Limitations

tDCS provides little spatial resolution, especially for stimulation with higher currents as used in the present study (Wagner *et al.*, 2007). Moreover, remote effects in subcortical and distant cortical regions cannot be excluded (Polania *et al.*, 2012). While this can be regarded a disadvantage to precisely map the anatomy subserving specific linguistic functions, it may well be an advantage for therapeutic purpose, since more than one region relevant for linguistic processing can be influenced. In the present study, we tested only mildly affected patients in the chronic phase after stroke, providing a proof-of principle for the involvement of the left MC in lexical decisions. It should be noted that different aphasic syndromes were prevalent in our patient cohort. This has particular relevance as it has been proposed that the influence of certain brain areas on recovery follows a hierarchical model in which lesion size/initial impairment and time from stroke are important factors (Hamilton et al., 2011). Indeed, patients with amnestic aphasia demonstrated less differences in accuracy between real and pseudowords than patients with Broca's aphasia or patients with mild residual deficits and consecutively showed no differences in accuracy for action words under anodal versus sham stimulation. However, because of the small sample size future studies are needed to test whether the observed effect varies in different types of aphasia, with different degrees of severity and/or time after stroke.

Abbreviations

(AAT) Aachener-Aphasie-Test, (ITI) intertrial interval, (LDT) lexical decisions task, (MC) motor cortex, (tDCS) transcranial direct current stimulation, (TMS) transcranial magnetic stimulation, (MEPs) motor-evoked potentials, (SLT) speech and language therapy, (rmANOVA) repeated measures analysis of variance, (OLP) "object-like" pseudowords, (ALP) "action-like" pseudowords, (RT) reaction time.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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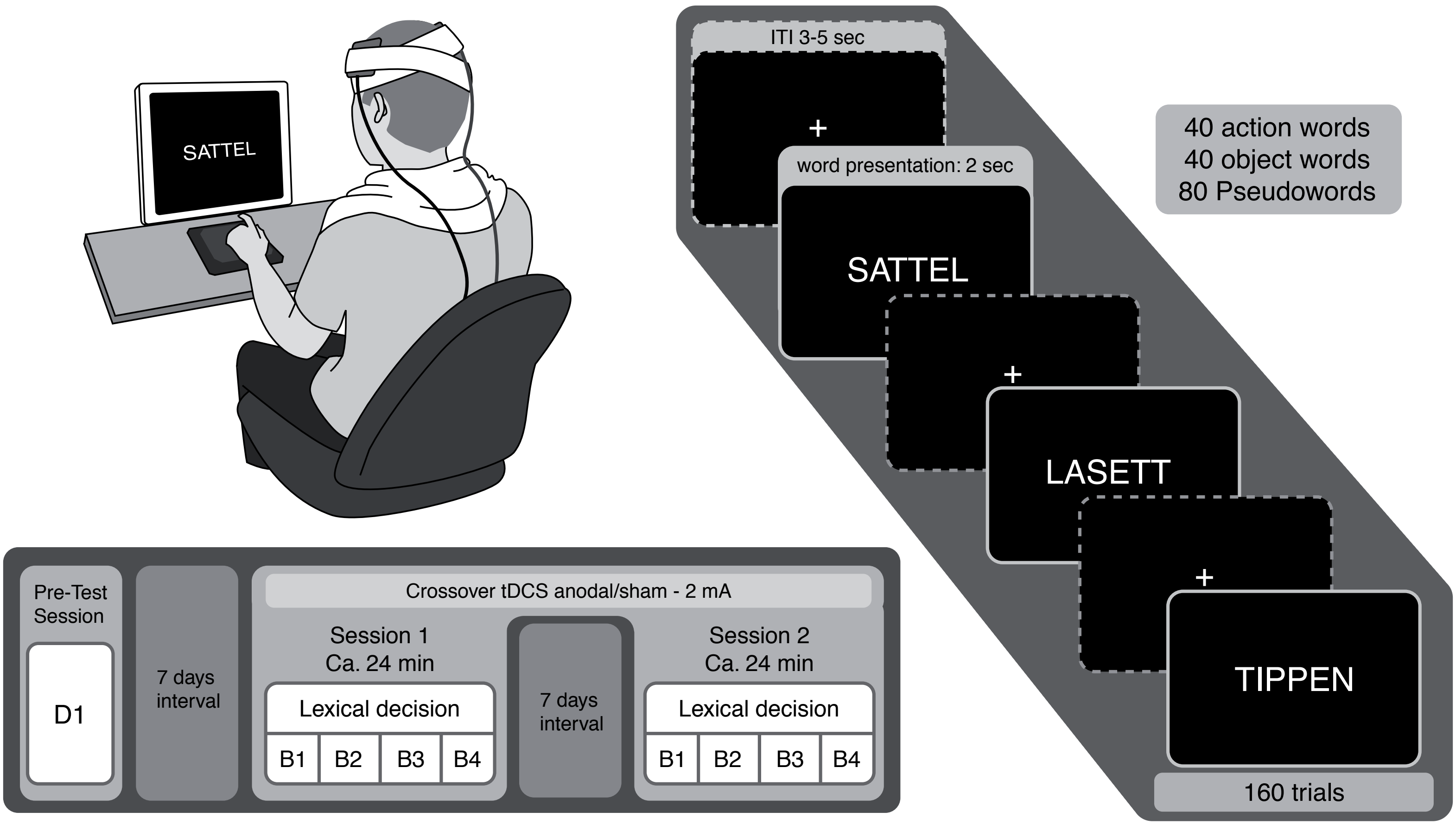
Figure legends:

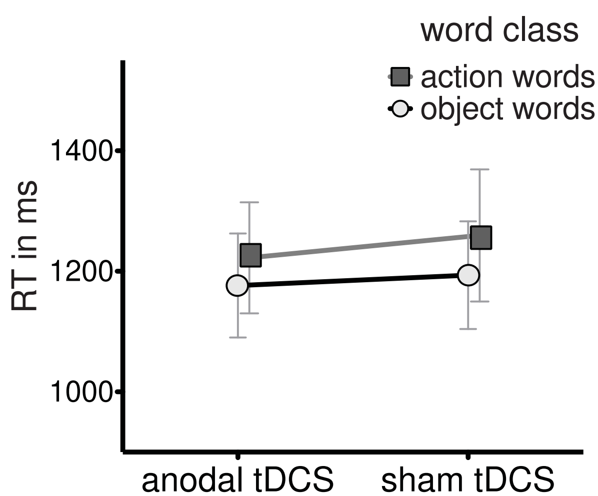
Figure 1 **Study design**. Patients had to decide whether the written stimulus was an existing German word or not in a lexical decision task (LDT). (A) Patients were seated in front of a flatscreen monitor and provided their answer by pressing different buttons on a custom-made button box (left button/“yes”, right button/“no”) with the left hand. Anodal or sham tDCS was applied with task onset and lasted for 20 min at 2 mA constant current in case of anodal stimulation. The stimulating electrode was positioned over the “hot-spot” of the left FDI. (B) The two types of stimulation (anodal/sham) were counterbalanced across sessions. Each session consisted of 160 trials and was subdivided into four blocks (B1-4) separated by 2 min breaks. The stimuli were presented for 2 s with an inter-trial interval (ITI) randomly varying between 3-5 s. Participants were familiarized with the task in a pre-test session D1. On each test session (D2 & D3), a simple reaction time test (sRT) was performed before TMS, right after tDCS stimulation onset (before block 1) and at the end of the task. The first and the second test session were separated by an interval of 7 days (D2 & D3). (C) Each test session comprised 40 action words and 40 “action-like” pseudowords, as well as 40 object words and 40 “object-like” pseudowords.

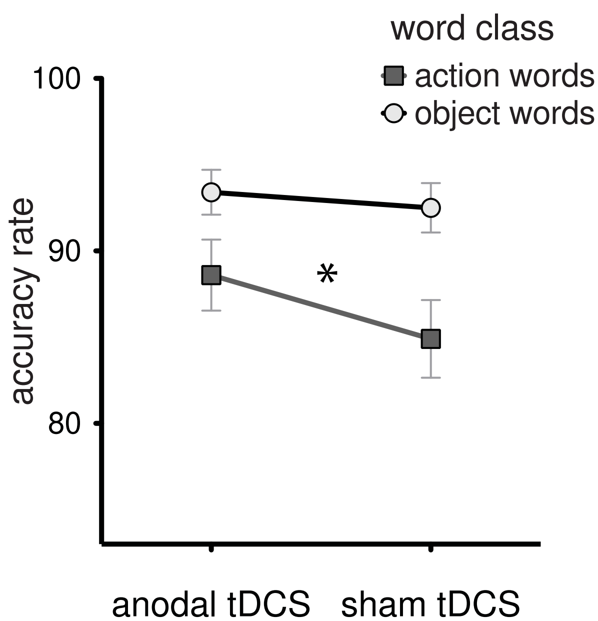
Figure 2 **Influence of anodal tDCS versus sham stimulation to the left MC on reaction times in the lexical decision task.** There was no significant main effect of stimulation on reaction times. Results for reaction times under anodal or sham tDCS subdivided for word class, RT = reaction time. Grey bars represent standard error of mean.

Figure 3: **Accuracy rates depicted as number of correct decisions in the lexical decision task.** Accuracy rates improved significantly for action words under anodal tDCS stimulation, whereas no such effect was present for object words. Grey bars represent standard error of mean.



SATTEL
ITI 3-5 sec
+
word presentation: 2 sec
SATTEL
+
LASETT
+
TIPPEN
160 trials
40 action words
40 object words
80 Pseudowords
Pre-Test Session
D1
7 days interval
Crossover tDCS anodal/sham - 2 mA
Session 1
Ca. 24 min
Lexical decision
B1
B2
B3
B4
7 days interval
Session 2
Ca. 24 min
Lexical decision
B1
B2
B3
B4


word class
action words
object words
1400
1200
1000
RT in ms
anodal tDCS
sham tDCS



word class
action words
object words
100
90
80
accuracy rate
*
anodal tDCS
sham tDCS

ID	Sex	Age (years)	Time since stroke (months)	Lesion location	Paresis	Type of aphasia (AAT)	AAT				
							Token Test	Repetition	Language	Naming	Comprehension
							points (percentile rank)				
1	**f**	51	27	Middle MCA territory, insular cortex & corona radiata	Yes, minor	Broca's aphasia	3 (95%)	132 (74%)	84 (95%)	106 (88%)	108 (95%)
2	**m**	69	20	Left parietal	Yes	Broca's aphasia 80%, Amnestic aphasia 19%	3 (95%)	135 (79%)	80 (89%)	108 (91%)	98 (81%)
3	**f**	49	25	MCA territory, basal ganglia, left frontal cortex & parietal cortex	Yes, severe	Amnestic aphasia 78%, Broca's aphasia 21%,	14 (75%)	142 (88%)	85 (95%)	100 (81%)	96 (76%)
4	**m**	69	9	Posterior MCA territory	No	Amnestic aphasia	0 (99%)	124 (66%)	85 (95%)	102 (59%)	103 (89%)
5	**m**	73	6	Left temporal	No	Residual symptoms, aphasia type not classifiable	0 (99%)	143 (89%)	81 (90%)	106 (88%)	100 (85%)
6	**m**	57	7	Left ncl. lentiformis	No	Residual symptoms, aphasia type not classifiable	0 (99%)	147 (96%)	89 (99%)	115 (89%)	110 (97%)
7	**m**	78	13	Anterior MCA territory, insular cortex & frontal cortex	No	Broca's aphasia	13 (76%)	135 (79%)	80 (89%)	90 (63%)	94 (73%)
8	**m**	50	3	Posterior MCA territory, parietal	No	Residual symptoms, aphasia type not classifiable	4 (94%)	143 (89%)	83 (93%)	116 (99%)	101 (86%)
9	**f**	62	36	MCA territory, left insular cortex, basal ganglia	Yes, severe	Amnestic aphasia	2	129 (71%)	85 (95%)	117 (99%)	105 (92%)
10	**m**	54	43	Left frontal cortex, Ncl. caudatus, basal ganglia	Yes, severe	Broca's aphasia	4 (94%)	131 (73%)	75 (80%)	110 (94%)	102 (88%)
11	**m**	48	5	Middle MCA territory, insular cortex	Yes, minor	Broca's aphasia	26 (51%)	65 (22%)	21 (30%)	35 (28%)	77 (47%)
12	**m**	47	41	Posterior MCA territory	No	Amnestic aphasia	7 (89%)	128 (70%)	83 (93%)	116 (99%)	110 (97%)
13	**m**	63	65	Left temporal & parietal & insular cortex	No	Amnestic aphasia	4 (94%)	126 (68%)	78 (86%)	106 (88%)	109 (96%)
14	**m**	56	42	Left temporal & insular cortex	Yes, minor	Residual symptoms, aphasia type not classifiable	0 (99%)	138 (83%)	86 (96%)	110 (94%)	118 (100%)
15	**m**	72	12	Anterior MCA territory, frontal & insular cortex	Yes, minor	Residual symptoms, aphasia type not classifiable	0 (99%)	147 (96%)	89 (99%)	115 (98%)	111 (98%)
16	**f**	73	16	Insular cortex & Ncl. lentiformis	Yes, moderate	Global aphasia	36 (36%)	37 (15%)	22 (31%)	0 (0%)	84 (58%)

Version 1			**Version 2**		
Action-related word	**English translation**	**Action-related pseudoword**	**Action-related word**	**English translation**	**Action-related pseudoword**
angeln	to angle	nalgen	backen	to bake	facken
basteln	to tinker	stabeln	bohren	to drill	rohben
dehnen	to stretch	nehden	fechten	to fence	lechten
ernten	to harvest	ternen	fischen	to fish	fuschen
feilen	to file	leifen	kegeln	to bowl, to skittle	gekeln
flechten	to weave	techteln	kellnern	to work as a waitress/waiter	renklern
formen	to form	morfen	klatschen	to applaud	faltschen
fuchteln	to brandish	tuchteln	klauen	to steal	lauken
hacken	to chop	kachen	klingeln	to ring (the bell)	glankeln
harken	to rake	krahen	kneifen	to pinch	feiknen
hobeln	to shape	bihlen	kramen	to rummage	ramken
kitzeln	to tickle	tickeln	kritzeln	to scrawl	tratzeln
kleistern	to paste	steiklern	lenken	to steer	fenken
kneten	to knead	kreten	nageln	to nail	gnalen
kochen	to cook	hicken	packen	to grab	tacken
kratzen	to scratch	trazken	pflastern	to pave	flipstern
kraulen	to tickle	laukren	pinseln	to brush	sinpeln
lochen	to pierce	fochen	pudern	to powder	dupern
meisseln	to chisel	seimseln	putzen	to clean	tuzben
melken	to milk	kelmen	quirlen	to wisk	lirquen
mischen	to blend	moschen	reiben	to rub	beiren
paddeln	to paddle	maddeln	rubbeln	to rub	burreln
prellen	to bounce	leppren	rudern	to row	durnen
quetschen	to squeeze	schertmern	rupfen	to pluck	prifen
raspeln	to rasp	sarpeln	scheuern	to scrub	reuschen
ritzen	to scribe	tirzen	schminken	to paint one's face	minschken
schalten	to switch	talschen	schubsen	to shove	buschern
schnitzen	to carve	tienschen	spachteln	to trowel	paschteln
schwenken	to swing	wiebschen	stechen	to sting	sechten
stanzen	to stamp	zansten	sticken	to embroider	ticksen
stempeln	to stamp	pemsteln	stochern	to poke	toschern
stopfen	to stuff	spoften	tippen	to tip	pitten
stricken	to knit	ricksten	trommeln	to beat the drum	mortteln
trocknen	to dry	ronckten	tunken	to dip	kunten
werken	to work	kewern	tupfen	to speckle	pfuten
wischen	to wipe	dischen	waschen	to wash	michten
wringen	to wring	gwirnen	wickeln	to wrap	lickten
zerren	to tug	firren	wuchten	to heave	trupten
zupfen	to tug	fuspen	zeichnen	to draw	neichzen
zwirbeln	to twirl	wirpfeln	zwicken	to twinge	wucksen

Version 1			**Version 1**		
Object-related word	**english translation**	**Object-related pseudoword**	**Object-related word**	**english translation**	**Object-related pseudoword**
abteil	compartment	taleib	becken	bassin	necker
auspuff	exhaust pipe	spauffu	brezel	pretzel	zerbel
besteck	culery	stebeck	brunnen	well	nebrunn
deichsel	drawbar	schiedel	deckel	lid	lecked
drucker	printer	ruckerd	droschke	hackney	schoderk
eintopf	stew	tienpof	flocke	flake	kofcke
fackel	torch	leckaf	Frachter	freighter	trafcher
geschirr	crockery	Rischger	gestell	shelf	stegell
gesteck	floral arrangement	seckteg	geweih	antlers	weihge
giebel	gable	leibeg	gletscher	glacier	schregelt
grotte	grotto	tregot	glocke	bell	kolget
hocker	stool	rehock	halfter	halter	trahlfe
hydrant	hydrant	trynard	joghurt	yoghurt	turgoht
jackett	coat	teckjat	kachel	tile	laheck
kleidung	clothing	dieklung	krippe	creche	prikep
knospe	bud	sponke	kristall	krystal	strillak
lappen	cloth	neppal	lumpen	rag	munlep
nachwuchs	offspring	schnuwach	planke	plank	klanpe
ordner	folder	ronder	polster	cushion	strelpo
parkett	parquet	krattep	ranzen	satchel	nerzan
pfanne	pan	fennap	schachtel	box	schelacht
pfosten	stake	stenpof	scharnier	hinge	seischarn
pritsche	plank bed	preischt	scherbe	shard	rebsche
reisig	brushwood	griesi	schlacke	cinder	leschack
riemen	lace	neimer	schranke	gate	narksche
sattel	saddle	lasett	speiche	spoke	piesche
schleier	veil	liescher	speisung	feeding	siepsung
schlitten	sledge	tilschent	splitter	splinter	stilpter
schnitzel	cutlet	tenschilz	stachel	spike	laschet
schuppe	scale	puschpe	stecker	plug	kerster
schwelle	barrier	wullsche	stockwerk	floor	twockerst
socken	socks	nescko	tablett	tray	lettalb
spange	clasp	ganspe	tempel	temple	lempet
brosche	brooch	schorbe	traktor	tractor	rotarkt
speicher	storage	reischep	tresor	safe	roster
stengel	stalk	lengest	trichter	funnel	rechtrit
verschlag	crate	schraglef	verdeck	canopy top	derveck
wecker	alarm clock	reckwe	wappen	emblem	seppan
wimpel	pennant	welmpe	Weiher	pond	hiewer
zwieback	rusk	waizbeck	zucker	sugar	rucher